Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Claim 1. (Currently Amended) A method ~~of~~ for monitoring cell differentiation comprising:

(a) culturing cells capable of differentiating into at least one particular cell type wherein said cells contain ~~containing~~ at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation, or maintaining a non-human animal comprising said ~~such~~ cells, under conditions allowing differentiation of ~~the~~ said cells; and

(b) determining the amount or activity of the reporter gene product ~~either~~ within a body fluid of said transgenic non-human animal or the cell culture medium of said cells.

Claim 2. (Original) The method of claim 1, wherein said recombinant nucleic acid molecule comprises at least one cell type-specific regulatory sequence operably linked to said reporter gene.

Claim 3. (Currently Amended) The method of claim 1 ~~or 2~~, wherein said cells ~~are or~~ are derived from stem cells.

Claim 4. (Original) The method of claim 3, wherein said stem cells are embryonic stem cells or multipotent adult progenitor cells (MAPCs).

Claim 5. (Currently Amended) The method of ~~any one of claims 1 to 4~~ claim 1, wherein said reporter gene product comprises a secretory leader sequence.

Claim 6. (Currently Amended) The method of ~~any one of claims 2 to 5~~ claim 1, wherein said regulatory sequence comprises a promoter ~~and/~~or enhancer element or both.

Claim 7. (Currently Amended) The method of ~~any one of claims 1 to 6~~ claim 1, wherein said cell type is selected from the group consisting of connecting fibroblasts, stromal cells, endothelial cells, glial cells, neural cells, neuronal cells, hematopoietic cells, smooth muscle cells, skeletal muscle cells, epithelial cells, and cardiac cells.

Claim 8. (Currently Amended) The method of claim 6 ~~or 7~~, wherein said promoter or said enhancer is selected from the group consisting of αMHC, MLC2V, VE-cadherin, Tie-2, Flk-1, Fit-1, GFAP, alpha-l-tubulin and collagen 2 promoter or enhancer.

Claim 9. (Currently Amended) The method of ~~any of claims 1 to 8~~ claim 1, wherein said reporter gene product is secreted alkaline phosphatase (SEAP) or alpha-amylase.

Claim 10. (Currently Amended) The method of ~~any one of claims 1 to 9~~ claim 1, wherein said recombinant nucleic acid molecule further comprises a selectable marker expressed by multi- or pluripotent cells.

Claim 11. (Currently Amended) The method of ~~any one of claims 1 to 10~~ claim 1, wherein said cells form cell aggregates or tissue-like aggregates derived from different cell types.

Claim 12. (Currently Amended) The method of ~~any one of claims 1 to 11~~ claim 1, wherein said cells form embryoid bodies (EBs).

Claim 13. (Currently Amended) A reporter gene construct for monitoring cell differentiation comprising [[a]] the recombinant nucleic acid molecule ~~as defined in any one of claims 1 to 12~~ of claim 1.

Claim 14. (Currently Amended) A cell ~~as defined in any one of claims 1 to 12 or~~ comprising a reporter gene construct of claim 13, wherein said cell is capable of differentiating into at least one particular cell type.

Claim 15. (Currently Amended) A cell aggregate of at least one cell type obtainable by the method of ~~any one of claims 1 to 12~~ claim 1.

Claim 16. (Currently Amended) A tissue ~~obtainable by the method of any one of claims 1 to 12 or~~ comprising said cell[[s]]of claim 14 ~~or a cell aggregate of claim 15~~.

Claim 17. (Currently Amended) An organ comprising ~~a tissue of claim 16, a~~ said cell of claim 14 ~~or a cell aggregate of claim 15~~.

Claim 18. (Original) An implant or transplant comprising an organ of claim 17, a tissue of claim 16, a cell of claim 14 or a cell aggregrate of claim 15.

Claim 19. (Original) A non-human animal comprising a reporter gene construct of claim 13, a cell of claim 14, a cell aggregate of claim 15, a tissue of claim 16 or an organ of claim 17.

Claim 20. (Original) A composition of matter comprising a reporter gene of claim 13, a tissue of claim 16, cells of claim 14 or a cell aggregate of claim 15.

Claim 21. (Currently Amended) An array comprising a solid support wherein said cells of claim 14, said cell aggregate of claim 15 or said tissue of claim 16 are attached thereto ~~and attached thereto or suspended thereon cells of claim 14, a cell aggregate of claim 15 or a tissue of claim 16~~.

Claim 22. (Original) An apparatus for analyzing the array of claim 21.

Claim 23. (Currently Amended) A method ~~of~~ for obtaining, ~~and~~/or profiling or both, a modulator of cell differentiation comprising:

(a) contacting a test sample comprising a cell of claim 14, ~~a cell aggregate of claim 15, a tissue of claim 16 or an organ of claim 17 or a non-human animal of claim 19~~ with a test substance; and

(b) determining the effect of the test substance on the amount of the reporter gene product or activity compared to a control sample ~~or animal~~.

Claim 24. (Currently Amended) The method of claim 23, wherein said contacting ~~step~~ further ~~includes~~ comprises contacting said test sample ~~or animal~~ with at least one second test substance in the presence of said first test substance.

Claim 25. (Currently Amended) The method of ~~any one of claims 1 to 12 or 23 to 24~~ claim 23, wherein a compound known to activate or inhibit the differentiation process is added to ~~the culture medium or animal~~ said test sample.

Claim 26. (Currently Amended) The method of ~~any one of claims 23 to 25~~ claim 23, wherein the test substance is a therapeutic agent.

Claim 27. (Currently Amended) The method of ~~any one of claims 23 to 26~~ claim 23, wherein the test substance is a mixture of therapeutic agents.

Claim 28. (Currently Amended) The method of ~~any one of claims 23 to 27~~ claim 23, wherein preferably in a first screen said test substance is comprised in and subjected as a collection of test substances.

Claim 29. (Original) The method of claim 28, wherein said collection of test substances has a diversity of about 10^3 to about 10^5.

Claim 30. (Original) The method of claim 29, wherein the diversity of said collection of test substances is successively reduced.

Claim 31. (Currently Amended) The method of ~~any one of claims 23 to 30~~ claim 23, ~~which~~ wherein said method is performed on an array.

Claim 32. (Currently Amended) The method of any one of claims 1 ~~to 12~~ or 23 ~~to 31~~, wherein said one or more cells are genetically engineered to (over)express or inhibit the expression of a target gene.

Claim 33. (Currently Amended) The method of ~~any one of claims 1 to 12 or 23 to 32~~ claim 23, wherein said one or more cells or tissue are contained in a container.

Claim 34. (Currently Amended) The method of ~~any one of claims 1 to 12 or 23 to 33~~ claim 33, further comprising taking [[3]] three or more measurements, optionally at different positions within the container.

Claim 35. (Currently Amended) The method of claim 33 ~~or 34~~, wherein said container is a well in a microtiter plate.

Claim 36. (Original) The method of claim 35, wherein said microtiter plate is a 24-, 96-, 384- or 1586-well plate.

Claim 37. (Currently Amended) A method of obtaining and manufacturing a drug which promotes or inhibits formation of specific cell types comprising the ~~steps~~ method of ~~any one of claims~~ claim 23 ~~to 36~~, wherein an enhanced or reduced level or activity of the reporter gene product is indicative for the drug.

Claim 38. (Currently Amended) A method of manufacturing an agent which supports wound healing ~~and/~~or healing of damaged tissue or both comprising ~~the steps of~~ the method of ~~any one of claims~~ claim 23 ~~to 37~~, wherein an enhanced level or activity of the reporter gene product is indicative for said agent.

Claim 39. (Currently Amended) A method of determining toxicity, preferably teratogenicity, embryotoxicity, chronic or acute toxicity of a ~~compound~~ test substance comprising ~~the steps of~~ the method of ~~any one of claims~~ claim 23 ~~to 37~~, wherein a reduced or enhanced level or activity of said reporter gene product is indicative for the toxicity of ~~the~~ said ~~compound~~ test substance.

Claim 40. (Currently Amended) The method of ~~any one of claims 23 to 39~~ claim 39, further comprising modifying said test substance to alter, eliminate ~~and/~~or derivatize a portion of said test substance thereof that is suspected of causing toxicity, increasing bioavailability, solubility ~~and/~~or half-life.

Claim 41. (Currently Amended) The method of ~~any one of claims 23 to 40~~ claim 40, further comprising mixing the substance isolated or modified with a pharmaceutically acceptable carrier.

Claim 42. (Currently Amended) A kit useful for conducting a method of any one of claims 1 ~~to 12~~ or 23 ~~to 41~~, containing for example a reporter gene construct of claim 13, a cell of claim 14, and standard compounds, like cell culture media, selection agents, detection agents for the reporter molecule and control samples.

Claim 43. (Currently Amended) A method of conducting a drug discovery business comprising:

(a) providing one or more assay systems of any one of claims 1 ~~to 12~~ or 23 ~~to 41~~ for identifying a modulator of cell differentiation; ~~and/or~~

(b) conducting therapeutic profiling of modulators identified in step (a), or further analogs thereof, for efficacy and toxicity ~~in animals of claim 19~~; and

(c) formulating a pharmaceutical preparation including one or more modulators identified in step (b) as having an acceptable therapeutic profile.

Claim 44. (Currently Amended) A method of conducting a target discovery business comprising:

(a) providing one or more assay systems of any one of claims 1 ~~to 12~~ or 23 ~~to 41~~ for identifying modulators of cell differentiation;

(b) ~~(optionally)~~ conducting therapeutic profiling of modulators identified in step (a) for efficacy and toxicity ~~in animals of claim 19~~; and

(c) licensing, to a third party, the rights for further drug development ~~and/~~or sales or both for modulators identified in step (a), or analogs thereof.

Claim 45. (Currently Amended) A modulator of cell differentiation such as growth and tissue formation promoting identified according to the method of ~~any one of claims~~ claim 23 ~~to 41~~.

Claim 46. (Currently Amended) A pharmaceutical composition for use in the modulation of cell differentiation comprising a modulator identified according to the method of ~~any one of claims~~ claim 23 ~~to 41~~.

Claim 47. (Currently Amended) A method ~~of~~ for making a pharmaceutical composition for use in modulating cell differentiation comprising mixing a modulator of cell differentiation identified according to a method of ~~any one of claims~~ claim 23 ~~to 41~~ with a suitable diluent or carrier.

Claim 48. Cancelled.

Claim 49. (Original) A vector comprising the promoter region of the mouse alpha myosin heavy chain gene or of the ventricular myosin regulatory light chain gene, and operably linked thereto a heterologous DNA sequence.

Claim 50. (Currently Amended) The vector of claim 49, wherein said promoter comprises the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 2, or a fragment thereof.

Claim 51. (Currently Amended) The vector of claim 49 ~~or 50~~, wherein said heterologous DNA sequence encodes a reporter or a selectable marker.

Claim 52. (Currently Amended) The vector of ~~any one of claims 49 to 51~~ claim 51, wherein said DNA sequence encodes secreted alkaline phosphatase protein (SEAP).

Claim 53. (Currently Amended) The vector of ~~any one of claims 49 to 52 comprising~~ claim 49, comprising the nucleotide sequence of SEQ ID NO: 3.

Claim 54. Cancelled